COMBINED MEMORANDUM TO THE NDA

NDA:	21-036
Drug and Indication:	Relenza® (zanamivir dry powder for inhalation) for treatment of influenza A and B viral infections
Dose:	10 mg twice daily for five days for use with the DISKHALER® Inhalation Device
Applicant:	Glaxo Wellcome, Inc.
Date of Submission:	October 26, 1998
Date of Memorandum:	July 15, 1999

The applicant has requested approval for zanamivir, an inhibitor of influenza virus neuraminidase activity, administered by oral inhalation using a lactose powder vehicle with the DISKHALER® inhalation device for the treatment of influenza A and B viral infections. In support of this indication, the applicant has submitted the results of phase 2 and phase 3 trials conducted in the North America, Europe, and Southern Hemisphere during respective influenza seasons. The principal studies enrolled 1588 patients ages 12 years and older with uncomplicated influenza-like illness, with symptoms present for two days or less. Of 1164 patients with confirmed influenza, 89% had influenza A and 11% had influenza B.

Based on discussions between the applicant and the Division, the primary endpoint was defined as time to alleviation of major influenza-like symptoms, which included temperature below 37.8^0 C, feverishness symptom score of zero, and symptom scores no greater than mild for cough, headache, myalgia, and sore throat, all maintained without worsening for the subsequent 24 hours. Because of the subjectivity of the endpoint and concerns that use of relief medications could confound measurement and interpretation of this endpoint, throughout the development process the Division has considered it essential that certain secondary endpoints provide information supporting the conclusions for efficacy.

A total of 2289 patients, ages 12 and older, received zanamivir across all studies and are included in the safety database.

This application was presented at a meeting of the Antiviral Drug Advisory Committee on February 24, 1999. Based on the presented information, the Committee voted against recommending approval at that time. The concerns raised at the meeting were associated with lack of demonstrated treatment effect in the North American study, magnitude of the

treatment effect, a need for more information regarding patients with underlying pulmonary disease and high-risk patients, and recurrence of symptoms following treatment. These concerns and other major issues of this NDA have been thoroughly discussed in the medical officer's review. It should also be noted that there were some misperceptions by some members of the committee that only domestic studies were acceptable for making drug marketing claims in the United States. Despite statements of correction from FDA participants, this concept recurred in various forms throughout advisory committee discussions.

The Division has considered the totality of the data from three prospective phase 3 clinical trials conducted in North America, Europe, and the South Hemisphere, as well as other supporting data contained in the NDA. Although the treatment effect appears limited and there is less evidence for efficacy in influenza B than in influenza A, when all efficacy and safety data are reviewed together, the results support the approval of zanamivir for the treatment of uncomplicated acute illness due to influenza. However, several aspects of this drug's development and approval merit comment:

Summary of data in support of efficacy

Treatment effects were not consistent across the principal phase 3 studies. The largest phase 3 treatment study conducted in the North America failed to demonstrate a convincing treatment effect. However, the other two principal trials demonstrated clinically meaningful and statistically significant treatment effects. The differences between studies were not conclusively explained, however, the variable magnitude of treatment effect may have depended on the amount of symptomatic relief medication used and familiarity with the use of device. The efficacy results calculated by the applicant are provided in the following table.

Difference between placebo and zanamivir, primary endpoint

	NAIB3001 (Southern Hemisphere; n=455, Flu + 321, high-risk 76)	NAIB3002 (Europe; n=356, flu + 277, high-risk 32)	NAIA3002 (North America; n=777, flu + 569, high-risk 109)
Median days to alleviation (flu +)	P 6.0 days, Z 4.5 days, p=.004	P 7.5 days, Z 5.0 days, p<.001	P 6.0 days, Z 5.0 days, p=.078
Median days to alleviation (all randomized subjects)	P 6.5 days, Z 5.0 days, p=.011	P 7.5 days, Z 5.0 days, p<.001	P 6.0 days, Z 5.5 days, p=.228
Median days to alleviation (high-risk)	P 8.0 days, Z 5.5 days, p=.048	P 11.5 days, Z 9.0 days, p=.178	P 6.5 days, Z 7.5 days, p=.710
Median days to alleviation (high-risk, flu +)	P 8.3 days, Z 5.0 days, p=.161	P 11.5 days, Z 9.25 days, p=.21	P 6.0 days, Z 6.25 days, p=.886
Median days to alleviation (flu negative)	P 7.0 days, Z 6.75 days, p=.486	P 7.0 days, Z 5.25 days, p=.551	P 5.0 days, Z 6.0 days, p=.712

Despite limited efficacy in the North American study, the Division determined that this application provides sufficient evidence of efficacy because:

- When a disease is usually self-limited and of a short duration (days) it is a more difficult task to demonstrate a difference between the treatment groups. The efficacy of this product, based on the previously noted efficacy parameters and the understanding that influenza is a self-limited illness, has been demonstrated in two well-controlled trials conducted in Australia, New Zealand, South Africa, and Europe. Although these data are from foreign studies, they were carried out in populations that would not be expected to differ substantially from the US population, in characteristics of influenza illness, or access to widely accepted aspects of general medical practice.

- The third phase 3 treatment study conducted in North America is inconclusive in itself; taken together with the other studies, it is compatible with a modest effect.

- The phase 2 studies, although smaller and/or using different preparations of the drug are also compatible with a real but modest treatment effect in both North American and non-North American populations.

- The treatment effect was not clearly different in patients with influenza A and B; however, because of a smaller number of patients with influenza B enrolled into these trials, there was less evidence in support of efficacy of zanamivir in the treatment of influenza B.

- Although not a part of the formal review of this NDA for a treatment indication (only safety data were presented at the Advisory Committee meeting), preliminary results from the community prophylaxis trial conducted in the United States, involving over a thousand patients, also provide support of zanamivir's activity against influenza A in North America.

- Some patients reported influenza-like symptoms after the primary endpoint was reached. Assessment of symptom rebound or recurrence has been addressed by the analysis of time to alleviation without subsequent rise of symptoms and by additional analyses such as the analysis showing that the proportion of diary cards indicated "non-alleviated" after the primary endpoint did not differ substantially between the treatment groups.

Although no direct comparison can be made with drugs reviewed on the basis of different study designs, the marketing applications for the two drugs previously approved for influenza A treatment (amantadine and rimantadine) provide some useful context regarding the difficulties of performing influenza studies and interpreting the results. These two drugs were approved on the basis of much smaller studies. The study participants were from limited populations. A variety of endpoints were used, which

were not always clearly defined prospectively. In addition, the two approved drugs for the treatment of influenza are active only against influenza A.

Tolerability of this product during the conduct of the clinical trials was generally acceptable; overall, reported adverse events were similar between zanamivir and lactose inhaled powder.

The concern about the safety of this product in high risk patients was also raised during the Advisory Committee meeting. The preliminary safety data from the ongoing treatment study in asthma/COPD patients suggest that some patients with underlying airway disease may experience decreases in FEV1 in connection with inhaled zanamivir administration. This information is incorporated in the Precautions section of the labeling for zanamivir and thereby, describes the potential risks for this patient population.

Public Health Considerations

Influenza infection causes significant morbidity and mortality each year. During the 1998-1999 influenza season in the United States, the percentage of deaths from 122 reporting cities exceeded the epidemic threshold for 12 consecutive weeks according to the Centers for Disease Control and Prevention influenza summary update.

Clearly, the armamentarium for the treatment of influenza is lacking. As of 1993, only two medications, amantadine and rimantadine have been approved for the treatment of influenza A. The lack of new influenza medications became more evident recently when a strain of influenza virus that was previously known to infect only birds was associated with human disease. At least seven confirmed, unusually severe cases of influenza A due to the H5N1 strain of influenza virus were identified in Hong Kong between May and December of 1997.

Infection with a new virus strain raises significant public health concerns. A new virus has the potential to cause global disease in the form of a pandemic. To prepare for such a challenge, it is important to have new therapies available. Ideally, these new therapies would have antiviral activity against multiple influenza A strains, as well as influenza B, and a different side effect and resistance profile than currently marketed products.

Neuraminidase inhibitors, such as Relenza (zanamivir for inhalation) represent a new class of antiviral agents for the treatment of influenza. The neuraminidase enzyme is involved in the prevention of aggregation of influenza virus particles on the surface of infected cells. The proposed mechanism of action of zanamivir for inhalation is via inhibition of viral neuraminidase with the possibility of alteration of virus particle aggregation and relaease.

With regard to resistance, the extent of the data contained in the NDA package are insufficient to fully characterize the risk of emergence of resistant virus with clinical use. However, the applicant has committed to the development and implementation of a resistance surveillance program.

Treatment effects of anti-influenza drugs are usually rather small because of the self-limited nature of the disease in the vast majority of patients. Even a small treatment effect may have large economic and public health consequences because of the huge impact that influenza illness has on the general population. Because zanamivir has a different mechanism of action and is active against both influenza A and B, there may be a public health advantage to having zanamivir available as part of the treatment for a disease causing such widespread morbidity.

Viral resistance

At present, available data do not suggest that emergence of resistance is a rapid event. However, monitoring for viral resistance in clinical trials was based on an enzyme-activity assay for which the clinical implications are not clear. Resistance was observed to emerge in vitro, after multiple passages and in one case of naturally acquired influenza B infection in an immunocompromised patient receiving a nebulized zanamivir preparation for about two weeks. The applicant should explore development of a cell-culture-based assay for determination of viral susceptibility/resistance to zanamivir and develop a program for surveillance of development of resistance to zanamivir. This program should incorporate the use of cell-culture-based as well as enzyme-activity assays, examination of any isolates available after prolonged as well as brief zanamivir exposure, assessment of antigenic variation of clinical isolates and relationship of this variation to zanamivir exposure, and exploration of clinical implications of zanamivir-induced and zanamivir-dependent variants.

Instructions for patients

In addition to efficacy of zanamivir for the treatment of influenza, it is important that patients be able to use the drug/device system effectively. The concern is that potential patients will have to learn how to use the delivery system immediately in the setting of acute illness. The issues of proper use and limitations with respect to use of the delivery system will be addressed in the Precautions and Dosage and Administration sections of the labeling for zanamivir. The applicant has also developed instructions for patient use that each patient will receive at the time a prescription is filled for zanamivir. In addition, as a part of Phase IV commitments, it was recommended that the applicant obtain systematic data on patients' use of zanamivir through conduct of a labeling comprehension study in patients with influenza.

Labeling and proposed Phase IV commitments

At the time of this memorandum, the only outstanding substantive issues include labeling negotiations with the applicant to provide clarifications regarding the magnitude of treatment effect, describe the population who may benefit from the treatment, and provide balanced information on the potential for adverse effect on FEV1 or peak expiratory flow rate in patients with underlying respiratory disease.

The proposed phase IV commitments are intended to address and provide additional information on a) the use of the device and improvement of instructions for patients, b) safety of zanamivir in patients with underlying respiratory disease, c) safety and efficacy of treatment in high-risk patient groups and pediatric patients, d) safety and efficacy of

zanamivir in North American patients, e) effects of treatment on interruption of influenza virus transmission or when zanamivir is used for re-treatment of influenza, and f) safety and efficacy of prophylactic use of zanamivir to prevent influenza A and B. In addition to safety and efficacy issues being addressed, the applicant was asked to provide a plan and timeline for development and implementation of a resistance surveillance program and provide plans and proposals for development of an acceptable cell-culture-based assay for monitoring viral susceptibility/resistance to zanamivir.

It is expected that these issues will be satisfactorily addressed by the time of the regulatory action.

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NDA 21-036
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